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The Boston Medical Quarterly

VOLUME 16, NUMBER 4 DECEMBER, 1965

THE TEST OF TIME. VIII.

Aphasia

NORMAN GESCHWIND, M.D.*

THE great majority of practicing physicians and medical students, and probably even most neurologists, tend to regard the aphasias as a mysterious part of medicine — bewildering in its complexity and known only to a few experts. Aphasia is, however, similar to other phenomena encountered by the physician. In common with these other phenomena its more advanced aspects will be known only to a few specially interested students, but certain long-tested basic principles are simple and useful clinically even in the hands of the average practitioner. It is my task here to present some of the fundamental clinical rules which have stood the test of time. Perhaps the most useful way to present these will be to cite some of the common errors which are frequently made by the beginner in this area.

One of the most common pitfalls is the patient who does not speak at all. Aphasics are in fact rarely speechless, and nearly alway produce a few words. The totally speechless patient is usually not aphasic, but rather either has lesions of the nervous system quite different from those which produce aphasia, or is suffering from certain psychiatric disorders. Aphasia in most instances manifests itself as *abnormal* language rather than as total absence of speech.

A second pitfall is the severely dysarthric patient, particularly the one with bilateral cerebral lesions who has the classic syndrome of "pseudo-bulbar" dysarthria. The slurred speech of such patients may be incomprehensible and this may lead the doctor who sees other evidence of cerebral pathology to misdiagnose him as aphasic. Unless the words can be made out clearly enough to ensure that the *language* of the patient is abnormal, one must be wary of diagnosing aphasia.

Assuming that the physician has convinced himself that the patient is aphasic, he must make some decisions as to the localization of the responsible lesion. The most common pitfall in this diagnostic decision is the use of the common teaching (which I mention only in order to reject it) that the patient with trouble speaking has "expressive" aphasia and has an anterior lesion in the brain, while the patient who has trouble comprehending suffers from "receptive" aphasia and has a posterior lesion. This teaching is only partially justified; thus it is correct that the presence of comprehension deficit implies a posterior lesion in the speech areas. The error in this approach however results from the assumption that there is only one type of disorder in the expression of speech and that impairment of expression invariably signals an anterior lesion. In order to establish a more useful rule one must distinguish two different kinds of difficulty in the production of speech. At one extreme are those patients who are

*Chief, Neurology Service, Boston Veterans Administration Hospital; Associate Professor of Neurology, Boston University Medical School.

grossly *nonfluent,* that is, who utter only a few words which are produced slowly, with great effort, and with disturbed articulation. Although patients of this type may produce correct single word responses, they are incapable of uttering longer grammatical sequences. Thus such a patient may describe the weather as "sunny," but asked to make a sentence may merely offer "sunny" again or may at best say, "Weather sunny." At the other extreme are those patients who have no shortage of words but who are on the contrary grossly *fluent.* They may produce many phrases which contain the small grammatical words and which have the rhythm and melody of correct speech. The speech of these patients tends to be circumlocutory, contains many incorrect words (paraphasias) and is remarkably empty of content despite the profuseness of the verbal output.

We may now give one of the cardinal rules of localization: *Aphasias of the fluent variety occur only with posterior lesions,* i.e., with lesions behind the Rolandic fissure and which involve either the lower parietal lobe or the posterior temporal lobe. While different lesions in this posterior area produce syndromes which vary in ways which are obvious to a more experienced student, for ordinary clinical purposes the recognition of these cases as having posterior lesions is adequate. In keeping with the fact that the lesions of the fluent aphasias are well posterior to the motor cortex, *most of these patients have no hemiplegia.*

While in the presence of a fluent aphasia one may confidently predict a posterior lesion, nonfluent aphasia presents a somewhat more difficult problem.

Anterior lesions, that is, lesions in the classical Broca's area, always produce nonfluent aphasias. Unfortunately some patients with posterior lesions may also be nonfluent. Therefore the presence of a nonfluent aphasia confronts the examiner with a more difficult diagnostic problem. In this situation the use of signs of damage to neighboring anatomic structures is of great help — in particular the presence or absence of a hemiplegia, suggesting damage to motor cortex. Thus *a patient with a nonfluent aphasia and a hemiplegia* will generally be suffering from *a lesion of Broca's area and of the adjacent motor cortex.* By contrast *a patient with a nonfluent aphasia who has little or no hemiplegia is probably suffering from a lesion of the posterior speech regions.*

Some patients of course have large lesions involving both the anterior and posterior speech regions. Such patients are said to have global aphasia and present themselves with the combination of *nonfluent aphasia, severe comprehension deficit, and hemiplegia.*

A further diagnostic error results from the failure to recognize the fluent forms of aphasia. A patient who suddenly develops fluent incomprehensible speech in the absence of a hemiplegia is quite likely to be regarded as "confused," and I have even seen a patient with such a syndrome who was thought to be suffering from a postoperative psychosis. It should be remembered that the great majority of patients with fluent incomprehensible speech are in fact suffering from focal lesions of the brain rather than from nonfocal toxic impairments or from psychiatric disease.

I have glossed over many details of great clinical interest and many challenging theoretical problems. Thus lesions of Broca's area always produce nonfluent aphasias. Why, by contrast, lesions of the posterior speech regions should sometimes produce fluent aphasias and at other times nonfluent aphasias is a matter of great interest. I will not go into the theoretical interpretation of these findings but will only pause to remind the reader that if he will take the time to reread and learn the few basic principles stated in this article, he will have acquired some simple and valid rules which have withstood the test of time in clinical practice.

(Dr. Norman Geschwind has just been appointed to lead the research team in the new Boston University Aphasia Research Center, the first such unit to have been established by the National Institute of Neurological Diseases and Blindness. With the help of a Federal grant of nearly one and one half million dollars, we hope that this unit will lead to great advances in our knowledge of Aphasia and its treatment.)

Editor

PROGRESS IN MENTAL HEALTH LEGISLATION*

WILLIAM J. CURRAN, LL.M., S.M.HYG.†

IT seems to me fitting and proper that one of the themes of this annual meeting of psychiatrists and administrators of psychiatric institutions should be "Progress in Legislation."

At this mid-point in the 1960's in America, it is apparent that in psychiatry — and in law — we are in the midst of revolution. The revolution in psychiatry is more known and more experienced by you than by me; I will not presume to comment on it directly. In law, the revolt is within the classic tradition of revolutions — it is a matter of fighting against intolerable abuses, a human striving for better things, for human rights and privileges.

A few months ago in Washington, I heard Dean Lomans of the University of California speaking about "the revolt of the clients." I agree with this fully. We see it clearly in law where our criminal clients and Negro citizens are leading the ways of change.

I think we can also speak of a "revolt of the patients" in psychiatry. It is most apparent in mental deficiency where parent organizations have become very powerful political forces and have demanded action in research and patient care in a long neglected field. We are seeing also the effects of self-help organizations in child psychiatry, alcoholism, and drug addiction.

The field of psychiatry is bound to feel the impact of the client revolts in such areas as social work, race relations and law enforcement.

None of us as professionals can any longer act in what *we* believe is the best interest of our clients or patients without consulting them fully on the proposed course of action or, as you might call it, the treatment of choice. More and more they may disagree with us and, in their concerted numbers, they may have their way. They may not be wise every time they do this — any more than we have been!

However, my assignment today is more specific than this. I am asked to review and to comment on "progress" in legislation in the mental health field.

First of all, this means I must narrow my scope from law in general to legislative matters. I will not speak of the law the judges are making in the courtroom. I will speak only of the law being made by the people, or, more technically, by the politicians, in the Federal Congress and the state legislatures.

Secondly, I suppose this means I should talk only about "progress" — which implies forward movement, improvement, and not merely change, which may be good or bad. It is amazing how much legislative activity this simple definition eliminates.

I will start first with the Federal level. Progress here in recent years in mental health is mainly fiscal in nature; the Federal Government setting up new programs of financial aid to mental health. The concentration on fiscal matters is a reflection, not only of the tax structure of the United States which places so large a proportion of available public funds on this level, but of the legal, or constitutional, structure of the United States which leaves so much law, what we call "the police powers" over public health, safety, welfare, and morals, on the state levels.

In this Federal spending area in the 1960's, the big change, the progress, in mental health legislation is the shift from almost total concentration on research and training to the support of *services*. This effort had its beginnings in the Joint Commission Report and saw Congressional approval first with the Kennedy legislation on community mental health. It brought with it also in 1963 (for the fiscal year 1964) demonstration project money for the improvement of the quality of patient care in state hospitals and for in-service training programs for state hospital personnel.

The big push here is undoubtedly in

*Speech prepared for delivery as the *Keynote* at the *Seventeenth Annual Mental Hospital Institute* San Francisco, California, September 28, 1965.

†Dean, Metropolitan College, and Director, MetroCenter, Boston University.

community mental health. The Congress, and the U.S. Public Health Service, are quite frankly and openly trying to lead the revolution in mental health.

The federal program is basically one of construction funds, at the beginning at least, with the Hill-Burton general hospital construction program, which was begun by Congress in 1946, as the model. The Hill-Burton formula of starting with requiring a statewide plan is now in full operation. The Mental Health Planning project of two-years duration ended in July, 1965. The Mental Retardation Planning Projects will continue another two years. This planning will be followed by federal funds for construction of comprehensive community mental health facilities.

In fact, the construction funds now overlap the planning phases and this has caused many difficulties. In 1965, new legislation provides operational money for a limited period of time.

But one does not get money without strings attached. The federal regulations on this development, this revolution, in mental-health care are quite evident. They spell out what is required for "comprehensive" community mental health service. They set minimum and maximum limits on population to be served. Even in the planning stages, federal regulations controlled the methods and procedures of the planning process, and to an extent much broader and deeper than was practiced under the Hill-Burton program upon which it was modelled.

In the first go-round, every single state plan for Mental Retardation planning which was submitted to the Public Health Service, all fifty, were *rejected* and returned for rewriting in accord with federal standards.

It should be understood that I *do* consider this "progress." These federal regulations are generally an expression of very good practice which should be followed in the states. However, it must be realized by mental health administrators in the states that when the federal government gets into the area of *services,* as distinguished from research and training, the philosophy of control is entirely different. In research and training, we see academic freedom respected and untrammelled discretion vested in principal investigators. This is not the case when it comes to service operations.

Coming up to 1965, other than a continuation of these programs, the most important single piece of legislation otherwise related to mental health on the federal level is undoubtedly the Medicare Act. This act breaks with tradition in the Social Security field by allowing some psychiatric care to be covered under its benefits. None of us really know as yet what this will mean. At a minimum, however, it should broaden the alternatives of patients in selecting resources for care.

Medicare is a quite ingenious piece of legislation. The history behind it, which began in 1948, is one of the most fascinating adventure, battle, and intrigue stories of the Twentieth Century. It catapulted organized medicine into one of the most active federal lobbying groups in our country. It changed the very constitution, the state-national structure, of the American Medical Association. At the end in 1965, the final act was much more far-reaching than its sponsors had ever hoped for, since it combined features of both the Democratic and the Liberal Republican bills. No one ever expected the latter bill to pass, let alone be added to the basic Administration bill.

We haven't seen the last of this legislation. It will have to be corrected and tinkered with for years to come. We must admit, however, that physicians of any kind, including the U.S. Public Health Service, have had very little to do with it. It is a welfare measure and the welfare and social-work people probably will control its administration. This is to the fault of the medical profession which refused to recognize its responsibility to take part in its development, even if they didn't agree with it.

Personally, I think the delay in the enactment of this bill over these nearly two decades may have been of greater benefit to medical care generally in the United States than we may think.

We can compare our experience to that of Great Britain where, in 1948, the British Parliament passed a very comprehensive

medical care act. Today that program is in serious trouble, and a large part of that trouble is due to the fact that the British concentrated over these years on patient care itself, on meeting the quantity of care demanded by the people, to the detriment of the need for construction of facilities and for research and training. In the first ten years of the British National Health Service, not a single new hospital was constructed in Great Britain. Only in the past two years has a serious effort been concentrated on getting some new facilities under way.

In the United States, on the other hand, in 1948, the same year as the passage of the British NHS, the American Congress passed the Hill-Burton Hospital Construction Act. This was our response to the medical needs of our people after World War II. Under that act, the single most significant piece of medical legislation ever passed in this country in my estimation, thousands of hospitals and other medical facilities have been built throughout this country and are still being built. This act was the forerunner of other capital investment programs by the federal government in medical research and training which have brought immeasurable benefits to all Americans.

While the British concentrated on meeting consumer demand, we put our federal dollars into capital development. Based on hindsight, it was a good decision. The post-war years have been decades of unprecedented prosperity. Most of our people, thanks to this prosperity, the growth of prepaid insurance and Blue Cross, have managed to meet their medical care needs. The exceptions have been the economically deprived and a significant portion of the aged. Now, we are moving to fill these gaps.

Had Medicare passed in this country in those early post-war years, we might never have made the sacrifices in quantity which would have been necessary to get the long-term capital development with which we are so richly endowed today.

I will turn now to some examination of progress in legislation in the states.

The very character of state legislation is different than the federal. It includes similar measures of fiscal content, but it embraces in wider scope such matters as mental hospital commitment laws, criminal laws, property laws, state-local responsibility laws, etc. In the broad field of mental health, there are statutes of significance in all of these areas.

Also, in discussing the states, we have the problem of quantity. There are 50 states with fifty legislatures all busily passing laws annually or biannually. Justice Oliver Wendell Holmes referred to the state legislatures as individual laboratories of social experimentation. But not every experiment works or deserves to be commented upon.

The most significant national trend in the states in mental health laws in recent years has been the passage of state community mental health service acts. These have been enacted in at least 15 states.

They have resulted in very large increases in state expenditures. By conservative estimate, state budgets for community mental health have doubled in the last two or three years, to over 75 million dollars per year. Local government support has increased in a similar way to over 50 million dollars per year.

These community mental-health acts follow a basic pattern. They set up community mental health boards, often on a county basis, with broad community-group and public agency representation. They establish a state, matching-fund, contribution to the local group to operate the services under certain state-wide minimum standards. Local initiative and operational autonomy is retained in the community boards. The New York and California programs are perhaps the best known. They have had some troubles, but judged on the basis of *quantity* of services rendered, they have grown successfully in recent years.

As far as quality of legislative drafting is concerned, the Minnesota Act has received the strongest commendation since the Council of State Governments has adopted this act as the suggested model for all other states considering similar legislation.

One of the most serious problems these states have had is that of integrating the state hospitals into the system of community mental health. Concentration on small clinics has made many of the planners feel that the huge, chronic care institutions have no

place in the new scheme of things. Others have left out the state hospitals just because they are totally supported by the state and these community programs are a joint, or partnership arrangement between local and state governments with the operational control being local. The states and the state hospital superintendents, perhaps, have been unwilling to turn over control of these institutions to local citizen boards.

Another problem with these acts has been the complicated system of state-local financing. Many states have had to increase the state share because of the failure of the local communities to raise, and to continue to raise, their share. The state legislatures, on the other hand, have been uncomfortable with the fact that the local communities can force increases in state expenditures without any action by the state legislature itself. This has caused the state legislatures to place arbitrary ceilings on total state contributions either state-wide or on a per-capita basis in each community. These ceilings have also proved unrealistic or unworkable at times.

In some states, such as Massachusetts, the whole scheme of state-local partnership is under critical scrutiny. Local governments in states such as Massachusetts just do not have the tax base to support an expansion of mental-health services. It is now almost totally a state responsibility. If this situation remains, the state hospitals can be integrated effectively into a reorganized system of mental health care. In fact, the Mental Health Plan for Massachusetts, just recently completed, would make most of these hospitals combination continuing care hospitals for larger population areas and also comprehensive, community mental health facilities for their more immediate population concentrations. The Massachusetts plan would give a great deal of operational control to local and regional citizen boards, but would keep ultimate responsibility in the state Commissioner of Mental Health with a budget almost totally state-supported. With state money, it is expected that the program will be more flexible than would be the case with a state-local partnership arrangement. More importantly, it also means that the poorer parts of the state, which would not be able to raise necessary local funds, will not be deprived of needed services thereby.

Some planners in Massachusetts consider the Community Mental Health Service Acts passed in the late 1950's to be *obsolete* now because of what we know in the mid-1960's.

With this, I hope, provocative remark, I would like to pass on to another major area of mental health legislative activity: the revision of the commitment, or hospitalization, laws in the various states.

In the existing laws we see vast differences among the states. Judged by almost any modern standard, the laws of some of the states are still extremely crude. They are not much more than criminal procedures with mental illness — or, more likely, "lunacy" or "insanity" — substituting for a criminal charge. Some states are still without emergency commitment procedures or other basic provisions. Many still have Lunacy Commissions composed of disinterested, unqualified political appointees.

Therefore, when we speak of legislative "progress" in this area, the improvements can be judged only in a relative manner.

Most worthy of note, perhaps, are the comprehensive revisions which have been enacted recently in a number of states including New York, Illinois, Ohio, Wyoming, Tennessee, and the District of Columbia.

In the *states,* each of these revisions has followed a similar pattern. They have liberalized hospitalization procedures to make access to care easier and freer in keeping with the trend to open hospitals and community care. They have removed the requirement of prior approval of a court before hospitalization for a non-protesting patient. The more recent revisions in Illinois and New York, passed in 1964 and effective this year, also installed what is called "informal admission." This is a form of voluntary admission with less formality in signing papers and where the patient can leave at any time he desires. Connecticut has also adopted this procedure. Some institutions in Massachusetts are using the method, but without legislative sanction.

Another feature of these laws is the retaining of the civil rights and capacities of

hospitalized patients in such areas as voting and making a will or a contract.

By contrast, the very comprehensive revision of the commitment laws in the District of Columbia, enacted just last year, is a tightening up of court controls and supervision of hospitalization and continued care of patients. This law provides for emergency hospitalization of only 48 hours before a court order must be sought. It retains what many consider an outmoded and unnecessary review procedure before a Commission on Mental Health. The new law takes discretion away from the mental hospital in controlling voluntary admissions. It installs a "right to treatment" law under which a patient can apparently be released from hospitalization if he can convince a court he is not receiving adequate treatment. Jury trials on commitment are retained. Court-appointed counsel is available in all cases. Notices and hearings are elaborately provided for. Periodic re-examination of all patients is required by law. Like the New York and Illinois laws, the civil rights of patients are retained and hospitalization no longer automatically means incompetency. However, the D.C. law places the question of incompetency on the shoulders of the chief of service at the institution after the hospitalization of the patient and also places responsibility on the hospital to re-evaluate some 6000 patients at St. Elizabeth's who were committed before the new law went into operation. An emergency amendment was necessary this year (passed in August) to correct a court interpretation of Section 9 (e) of the new law which would have discharged 1200 incompetency committees appointed by the courts to care for the property of patients committed before the act was passed. These people would have been left entirely without protection for their property had the amendment not been passed.

The new D.C. law achieves quite a bit of good, but is largely relative good. The prior law was among the most primitive in the country. Voluntary admissions have increased under the new law, although the reasons for this are multiple. There is no doubt, however, that the new law emphasizes legalistic considerations and imposes a quite elaborate protective system around hospitalization.

It is important to note the origin of the new D.C. law. Unlike the law in most states, it was not advocated by mental health professionals or lay mental health organizations. It was the product of lawyers and others interested mainly in constitutional civil rights. Civil rights groups are becoming more and more interested in the commitment laws. They can be a serious obstacle to the efforts of mental health people to make treatment easier to obtain and communication between hospital and community freer and more open. In some areas, these groups are, in my judgment, on sound grounds constitutionally and many of the provisions they support, such as periodic re-evaluation, are quite commendable.

It is ironic that the mental health movement may find itself attacked on the left by the civil rights advocates and on the far right by the John Birch Society and its strange bedfellows. My only fear is that the mental healthers will withdraw from the fray in complete confusion. All of us are so used to fighting in lonely battles where we were always in the right, with God and the poor always on *our* side. Our only defeats were by the fiscal conservatives who said merely there wasn't enough money to go around.

Now, in this new era, we may have other opponents.

We have chosen to enter the community and we may get our lumps in the course of it.

There are so many other things to talk about — psychiatry's significance to law is ubiquitous. I would choose only one other area: criminal punishment, the price society exacts for acting out destructively — and getting caught.

The change, the progress, in this area by legislation in recent years is not very great from a psychiatric viewpoint, I am afraid.

The assassination of a young president and the vast and devastating public grief that followed it, with the bizarre, vengeful, public murder of Oswald by Ruby which accompanied it — and then that public spectacle of the Ruby murder trials in Dallas — none of these events would seem to

have had any effect in changing the rules of criminal responsibility in this country.

There have been a few changes unassociated with these public events. New York State has this year adopted the American Law Institute test of criminal responsibility. The change in New York is not very significant. New York's law and practice was particularly backward and the A.L.I. test is quite conservative.

The Ruby trial has resulted in some legislation. It is in this "public" environment I have been stressing. It seems that the American Bar Association and our legislatures may finally be getting around to imposing some restrictions on mass-media coverage of criminal arrests, police charges, and criminal trials. The events of Dallas seem to have turned enough stomachs finally to get action. I believe there is some psychiatric relevance in this legislation. I don't go quite as far as some psychiatrists in giving credit to the public "show of violence" as a cause of crime, but I'm sure it is important. There is no doubt of its importance in the fairness of the trial or in protecting the security of criminal prisoners.

The only legislative progress I have seen of real significance in recent years in criminal responsibility is the change in the narcotic drug addiction laws. Very important states, particularly California, New York, and Massachusetts have adopted sweeping changes which allow psychiatric treatment and follow-up programs in the community to substitute entirely for a criminal penalty where a person charged with crime is a drug addict. A number of bills are now before Congress to enact a similar change in the Federal narcotics law.

These laws are the ultimate in recognizing addiction as a disease and not a crime: to elect to treat the disease rather than punish the crime. The significance of this step is underscored if we recall that the penalties for narcotic drug traffic and use have been the most severe — the most *savage,* in the view of many — on all of our statute books; more severe in many jurisdictions than murder. This, then, is progress. Change in the face of failure, perhaps; the previous methods were failing to cope with the drug menace; but, nevertheless, *progress.*

There is still so *much* to do in the mental health laws of America. A great deal of improvement is needed. Mental healthers will have to stay in the battle of legislation for many years to come.

One of the major troubles in this field in my opinion is that it has been *over-legislated* during the past 100 years.

Mental illness is the most legally regulated disease in America.

It is defined in the law literally dozens of times for dozens of purposes. The law tells us what "mental illness" is and sets up legal machinery to get treatment, or not get it, and also, in its infinite wisdom, adjudicates "return to normalcy."

One of our tasks in the future, in my opinion, is taking a good deal of this law *out* of the mental health field, returning more of this subject to private determination. This, it seems to me, is what a great deal of our recent progress in legislation signifies. It is what "informed admission" means, and what "open hospitals" mean and what allowing mental patients to *retain* their civil rights when hospitalized means. It is taking the legal significance out of the transaction. For informal admission, it means admission as in any other medical situation without a formal legal procedure. For open hospitals it means no legal controls being exercised over the coming and going of the patients. For retaining civil rights, it means that entering a mental hospital no longer *automatically* has legal significance in the *loss* of those rights.

Legislative battles can be won, progress can be achieved, by removing laws, by reducing laws, just as much as by enacting new laws in new fields.

We now live in a huge network of mental health laws, a veritable jungle of provisions tangled among other provisions. I advocate cutting through some of this constant overgrowth of *laws* and *laws* and *laws* to clear the ground for the natural movement of people, even mentally sick people. Certainly we have learned that every time we have removed shackles from the mentally ill they have improved. I believe this is also true of some of these unnecessary legal shackles. It will take nerve. We will be opposed.

We will have cannons to the left of us, and cannons to the right of us like the brave 600 in the valley of Death. We should remember that Tennyson said of them,

"When can their glory fade?
O the wild charge they made!"

Let it be said of us. Our cause is as great.

CHROMOSOME TRANSFER IN CONJUGATION OF ESCHERICHIA COLI K-12*

RICHARD J. SAMAHA†

NATURE OF CONJUGATION IN ESCHERICHIA COLI

IN 1946, Lederberg and Tatum made the interesting discovery that genetic material could be transferred from one bacterial cell to another giving rise to zygotes or recombinant cells. Davis, in 1950, provided conclusive evidence that direct cell to cell contact was necessary for this transfer process to take place. The first indication of a sexual differentiation between cells participating in this mating process was made by Hayes[1] when he observed that one cell was acting as a donor and the other as a receptor of the genetic information. Subsequently, it was discovered that an infective factor, called F (fertility), was responsible for a bacterium acting as a donor, F^+.[2] The acceptor strains, F^-, were lacking the F factor. The sex factor could be transferred with high efficiency from donor to acceptor cells.[3,4] Crosses between F^- cells were sterile. Another type of donor called Hfr (high frequency of recombination) was discovered among stocks of F^+ cells. These Hfr donors gave a genetic recombination rate 1000 times greater than that of an equivalent F^+ strain when crossed with F^- cells. The recombinant cells from Hfr and F^- crosses were always F^- not having received the sex factor. The Hfr donors did not convert F^- cells to either F^+ or Hfr. Later, Hayes[5] showed that the Hfr cells donate at high frequency only a restricted segment of the chromosome and that the recipients are always F^-.

The exact nature of gene transfer by Hfr strains during conjugation with F^- strains was elucidated in a series of experiments by Wollman and Jacob.[6,7] Hfr chromosomal transfer was found to proceed in an oriented fashion such that one particular extremity, O (origin), is always the first to penetrate the receptor cell. The gene loci enter the acceptor cell in a linear ordered sequence, depending upon their fixed location on the bacterial chromosome. During chromosomal transfer, spontaneous ruptures occur limiting the segment of chromosome received by the F^- cell. Thus a genetic character located toward the distal end of the chromosome has a smaller probability of being transferred.

At this same time, another critical discovery was made by Jacob and Wollman[8] when they found that recombinants appearing in F^+ x F^- crosses were the result of spontaneous Hfr mutants present in the F^+ population. These Hfr mutants were isolated and crossed with various F^- strains to determine the order in which they transferred their genetic markers. Each Hfr mutant was found to differ in that segment of chromosome donated at high frequency and in the order in which the genetic markers were transferred.[9] However, it was found that although the Hfr strains differed in the order of transfer of genes to receptors, the linkage relationship of the various markers remained the same. From these latter results, Jacob and Wollman concluded that the genetic linkage map of the Hfr chromosome has the form of a closed circle. The F^+ chromosome was assumed also to be a continuous linkage group. Hfr mutations presumably arose from the reversible insertion of the sex factor into the circular F^+ chromosome. Mutations from the F^+ to the Hfr state, therefore, resulted in the conversion of the closed F^+ chromosome into a linear structure having an origin, O, and

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†Department of Biochemistry, Boston University School of Medicine, Boston, Massachusetts.

the attached sex factor at the distal extremity.

The transfer of the chromosome from the Hfr to the F^- cell can be divided up into several stages.[10] 1. Collision: Collision between the donor and receptor bacteria is the first step in conjugation. This interaction between the two parental organisms appears to be random with no specific factors involved. The rate of collision has been determined to be proportional to the concentration of the parent strains.[11,12] 2. Effective Contact Formation: An effective mating pair has been defined as "a specific pair in which all the conditions necessary for genetic transfer has been achieved."[13] The specificity of contact probably depends upon the structural and surface properties of the donor bacterium.[14,15] The formation of an effective union requires the synthesis of a conjugation tube (bridges of cellular material) that unites mating pairs.[16] The chromosome of the Hfr is presumably injected through the conjugation tube into the receptor cell. 3. Chromosome Transfer: Once effective contact between mating pairs is made, the Hfr begins to "mobilize" its chromosome in preparation for transfer[17] and generate energy needed for the transfer process itself.[18] Transfer of the chromosome proceeds at a constant rate until interrupted by environmental changes, such as lowering the temperature or drugs which inhibit energy production. By treating the mating pairs in a blender to mechanically separate them[6] or destroying the male with an excess of virulent bacterial virus,[11] it has been demonstrated that genetic markers appear in recombinant cells at specific times and in a sequence that corresponds to their linear genetic arrangement on the chromosome. Recent experiments have shown that only DNA with little or no RNA or protein is transferred from donor to receptor cell.[19]

STRUCTURE AND FUNCTION OF F

The sex factor (F) is a DNA containing structure approximately 2 per cent of the size of the bacterial chromosome.[20] Once inside the cell, the sex particle is able to multiply independently of the chromosome.[21] However, recent evidence suggests that sex factor replication becomes equilibrated with that of the host chromosome and that there exists normally only one sex factor per chromosome.[20,22] *Escherichia coli* is a haploid organism containing several genetically identical chromosomes.[23,24] Hirota[25,26] has demonstrated that acridine dyes can prevent the multiplication of the autonomous sex factor in the F^+ cell while replication of the host chromosome is unaffected. This experiment suggested that the two genetic units, chromosome and sex factor, have independent controlling systems of duplication.

Contact between donor and receptor cells is dependent upon the surface properties of the male strain. Cells possessing the sex factor have been shown to develop a specific surface antigen.[15] Following contact, the union between parent strains involves the formation of a cytoplasmic bridge, which is observable by electron microscopy.[16] This process of union between cells and subsequent mobilization with transfer of the donor chromosome is dependent upon the expenditure of energy via the tricarboxylic acid cycle by the donor bacterium.[27,28] Presumably, the sex factor determines not only some of the biochemical properties of the cell surface but also is the controlling element regulating the synthetic activities of the donor cell related to sexual conjugation.[29]

STRUCTURE AND REPLICATION OF THE BACTERIAL CHROMOSOME

Refined genetic analyses have demonstrated that in *E. coli* strain K-12, the chromosome of the F^+ and F^-[10] and the Hfr[30] is in a closed circular linkage group. Cairns[31] has gently extracted tritiated thymidine labeled DNA and prepared autoradiographs of the isolated genetic material. The resultant photographs provided good evidence that the chromosome of *E. coli* consists of a single piece of double stranded DNA in the form of a closed circle of about 1000 μ in length. This picture of the bacterial chromosome is in accord with accumulated genetic information on the structure of the bacterial chromosome.[32]

Yoshikawa and Sueoka[33-35] have presented a series of ingenious experiments dealing with a strain of *Bacillus subtilis* that

would suggest that chromosomal replication begins at a fixed starting point and proceeds down the length of chromosome until the genetic material is duplicated. In other words, each cycle of replication begins and ends at the same gene locus. In a study of chromosomal replication of two Hfr strains of *E. coli* K-12, Nagata[36,37] obtained evidence that in the nonconjugating Hfr, replication of the chromosome is sequential starting from the integrated sex factor region and proceeding to the origin (designated as leading end in transfer). Further support for a polarized mode of chromosomal replication came from Cairns' work on the autoradiography of replicating DNA from an Hfr and F^- strain of *E. coli* K-12.[29,38] Autoradiographic pictures revealed that replication proceeds from a single point and in one direction until the chromosome is duplicated. Interestingly, the chromosome remained in the form of a closed circle while replicating itself.

Jacob and Brenner[39] have proposed the following model for the molecular control of DNA replication in bacteria. A genetic element capable of independent duplication such as a sex factor or chromosome is regarded as a unit of replication or "replicon." Each replicon contains two genetic loci necessary for its replication. One locus (a structural gene) controls the synthesis of a specific cytoplasmic element, called an initiator, which acts in a positive manner on a second locus, designated as the replicator, to allow the duplication of the DNA starting at the replicator segment.

The Hfr chromosome with its integrated sex factor provides an opportunity to study direct interaction between the two replicons. As mentioned previously, Hirota[25] has shown that acridine orange inhibits replication of the autonomous sex factor but not the F^+ chromosome. Interestingly, under similar conditions of dye treatment, replication of the Hfr chromosome is also resistant to acridine orange. In addition, Cuzin and Jacob[40] have described bacteria that contain mutant sex factors which are unable to multiply at elevated temperatures that do not affect chromosomal duplication. When integrated into the host chromosome forming an Hfr, the sex factor segment is able to replicate regardless of the temperature. These results have suggested that in the Hfr state, the genetic elements of the bacteria are replicated under the control of the chromosomal replicon. However, Nagata's[34] study of chromosomal duplication in his strains of Hfr suggested that the integrated sex factor replicon controlled replication. I shall return to this interesting point when I discuss some of my experimental results of chromosome transfer using Nagata's Hfr strain.

CHROMOSOME TRANSFER DURING CONJUGATION

Studies have shown that the chromosome of the nonconjugating Hfr is in the form of a closed circle. In order for transfer during conjugation to take place, the chromosome of the Hfr must break at the site of the sex factor into a linear structure. The transfer process itself depends upon the movement of the chromosome from the Hfr to the F^- cell. The interaction between integrated sex factor and bacterial chromosome leading to genetic transfer during conjugation has been the subject of much recent work.

Nagata's proposal that replication of the Hfr chromosome proceeds from the integrated sex factor to the origin leads to the conclusion that the last part of the DNA molecule to be duplicated is the first to be injected during conjugation. Following this conclusion, Bouck and Adelberg[41] have suggested the following model of chromosome transfer. Each Hfr cell in a given population is in a different stage of the replication cycle just prior to mating. When the Hfr conjugates with an F^-, the last part of the male chromosome being formed breaks into an open structure rather than joining in a circle. This unattached end becomes the origin as the DNA is transferred to the recipient, leaving behind the chromosome used as the template for duplication. In this scheme, DNA synthesis is required prior to initiation of transfer but not for the injection process itself. In support of this suggestion that already duplicated chromosomes can be mobilized and transferred is the finding by Suit et al.[42] that chromo-

some transfer can occur without accompanying DNA synthesis.

Recent work by Ryter and Jacob[43] which revealed that a part of the bacterial chromosome is connected to the cell membrane has prompted Jacob et al.[29] to suggest that this attachment in the Hfr occurs at the site of the integrated sex factor. In their model for genetic transfer, Jacob et al. propose that the Hfr and F^- conjugate at an area bordering the site of chromosomal attachment. This interaction between donor and recipient stimulates duplication of the chromosome by the sex factor replicon. One of the DNA duplexes being formed is then driven into the F^- cell while the other remains in the Hfr. In contrast to the Bouck and Adelberg model, the first marker to be replicated is the first to be transferred; and thus, the orientation of DNA replication in the two schemes is exactly opposite. As a key test of whether the sex factor replicon becomes activated at conjugation, Jacob et al.[29] took advantage of the finding by Hirota that acridine orange inhibits sex factor replication and performed matings in the presence of acridine orange with their Hfr strains. They found that gene transfer was inhibited in the presence of the dye as predicted from their model.

In this report, I will present some of my experimental work done on the effect of acridine orange on chromosome transfer in Hfr strains. One of the Hfr strains used in this study was the donor studied by Nagata. During the course of my work, I found this latter donor to have unusual chromosome transfer kinetics not previously reported.

MATERIALS AND METHODS

STRAINS OF BACTERIA

The bacteria used in these experiments are all derivatives of *E. coli* strain K-12. Hfr strain HfrC was obtained from Dr. C. Folsome and is a derivative of the Hayes HfrH.[11] Hfr strain HfrCS101 was obtained from T. Nagata. F^- strain A288 was obtained from Dr. S. Luria. The donor bacteria (Hfr) transfer their genetic markers to the recipients (F^-) in the following order: HfrC, origin — $Threonine^+$-$Leucine^+$ — $Proline^+$ — $Lactose^+$; HfrCS101, origin — $Lactose^+$ — $Proline^+$ — $Leucine^+$-$Threonine^+$. F^- strain A288 has the genetic composition, $Lactose^-$, $Threonine^-$, and $Leucine^-$. Ability to synthesize an amino acid or utilize a carbohydrate is indicated by a + and inability to synthesize or utilize by a −. I have described here only the pertinent genetic markers used in this study. For a full description of the genetic map of *E. coli* see the paper by Taylor and Thoman.[44] The males used in this study are sensitive to the bacteriophage T_6 and streptomycin while the F^- strain is resistant to both. All the bacterial strains were maintained on nutrient agar slants and their genetic composition checked at regular intervals by the technique of replica stamping.[45]

MEDIA

Minimal media used throughout these experiments had the following composition per liter of distilled water; $K_2HPO_4 \cdot H_2O$ — 8.7 gm., $KH_2PO_4 \cdot H_2O$ — 6.8 gm., $CaCl_2$ — 0.005 gm., $FeSO_4 \cdot 7H_2O$ — 0.00025 gm., $MgSO_4 \cdot 7H_2O$ — 0.1 gm., NH_4Cl — 1 gm., the pH was adjusted with NaOH or HCl.

The composition of the broth media used in the mating experiments contained per liter minimal media; tryptone 10 gm., NaCl 10 gm., yeast extract 5 gm., and glycerol 0.5 gm.

Solid media used in the selection of recombinants and scoring of genetic markers contained per liter of minimal media at pH 7.2; carbon source (glucose) or fermentation marker (lactose) 0.5 gm.; thiamine 1 mg.; the amino acids were added as needed by the F^- or left out if to be selected for in the recombinant as follows, leucine 40 mg.; threonine 80 mg.; methionine, arginine, histidine and proline 80 mg. Streptomycin was added at a concentration of 200 mg. per liter. For solid media 20 gm. per liter Difco agar was added and for soft agar, 6.0 gm. per liter.

Sugars were sterilized separately and then added to autoclaved media. Lactose and thiamine were sterilized by passage of stock solutions through 0.45 μ millipore filters.

PREPARATION OF BACTERIOPHAGE T_6

Bacteriophage T_6 (obtained from Dr. C. Folsome) was added at a multiplicity of 1

phage per 10 bacteria to *E. coli* B growing exponentially in one liter of media containing glycerol, casamino acids, and salts prepared after Fraser and Jerrel.[46] The growth of the phage-bacteria mixture was followed in a Klett spectrophotometer until a sudden drop in the O. D. of the media indicated lysis of the bacteria. At this point, chloroform was added to the media to lyse any remaining bacteria; and the phage were isolated by centrifuging the broth at 5,000 rpm for 15 minutes to sediment the cellular debris. The yield of phage in the supernatant was usually about 2-3 x 10^{11} per ml. The supernatant was then spun at 20,000 g. for 60 minutes in a table Lourdes centrifuge. The pellet containing the phage was taken up in tryptone broth (10 g tryptone, 5 g NaCl [biological], 100 ml. distilled H_2O) and stored in stock solution of 2 x 10^{11} T_6 per ml. over chloroform at 4°C. A single preparation of phage was used in all these experiments and was assayed at frequent intervals by the method of Adams[47] showing no loss in titre.

Mating Conditions

Three ml. of broth media at pH 7.2 were innoculated from agar slants and grown overnight at 37°C. 0.2 ml. of the overnight culture were inoculated into 20 ml. of fresh broth at pH 6.3 in an Erlenmeyer flask fitted with a Klett tube side arm so that growth could be followed directly in a Klett spectrophotometer.[48] Cells were grown to a concentration of about 1-2 x 10^8 cells per ml. in the exponential phase of growth. To start the mating experiment, 1 ml. of Hfr cells were mixed in 9 ml. of F^- cells in a prewarmed 500 ml. Erlenmeyer flask and mating mixture incubated without shaking at 37°. The mating was interrupted at intervals by adding one ml. of phage (titre about 2 x 10^{10} T_6/ml.) to 1 ml. samples giving a multiplicity of about 1000 phage per 1 Hfr.[11] The phage-bacteria samples were incubated for 15 minutes at 37°C. with shaking and then diluted in Difco broth. The diluted samples were mixed in duplicate in warmed soft agar and poured onto solid agar plates. As a control, F^- cells were treated with phage in the same manner, diluted and plated. At the high multiplicity of phage infection, the sensitive Hfr cells are disrupted almost immediately by lysis from without.[49] The poured plates were incubated from 24 to 48 hours and the recombinants counted at that time.

Acridine Orange Mating

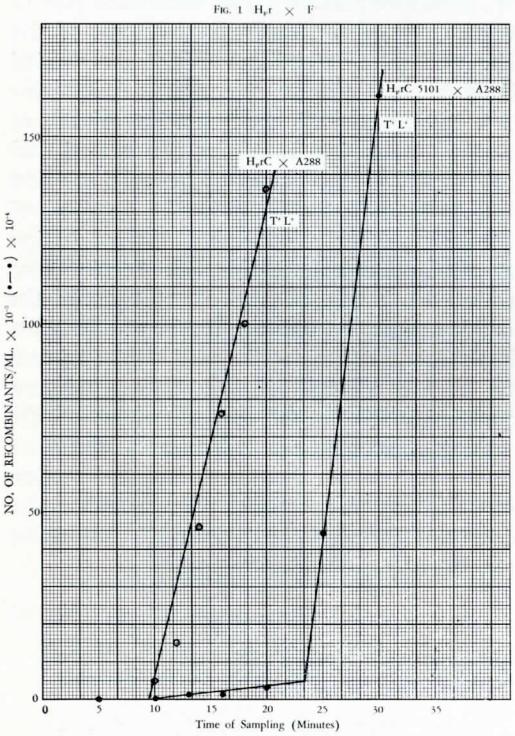
Cells were grown overnight as usual and 0.2 ml. were inoculated into 20 ml. of broth media at pH 6.3. When the bacteria (F^- and Hfr) reached a concentration of about 2 x 10^8 cells per ml., the cultures were transferred to sterile, capped polyethylene Lourdes centrifuge tubes and spun at 5,000 rpm for 5 minutes. The bacterial pellets were taken up and dispersed in fresh pH 8.0 broth warmed to 37°C. Then, 5 ml. aliquots of the Hfr and F^- broth solutions were added to prewarmed 125 ml. and 250 ml. flasks respectively and incubated for 15 minutes at 37°C. Similarly, 4.75 ml. of the Hfr and F^- solutions to which were added 0.25 ml. of an acridine orange (AO) solution giving a final concentration of 30 μg AO/ml. were incubated in prewarmed 125 ml. and 250 ml. flasks. The AO solution was prepared according to the method of Hirota.[25] After 15 minutes preincubation at 37°C., 0.5 ml. of the Hfr solution was added to 5 ml. of the F^- culture in the 250 ml. flask to start the mating. One mating mixture contained 0 μg AO/ml. and acted as the control for the mating mixture containing 30 μg AO/ml. Samples of the mating mixtures were taken at 45 minutes and treated as described in the section on Mating Conditions. Acridine orange does not interfere with immediate lysis of the male by the bacteriophage.[50]

Results

Kinetics of Gene Transfer in the Hfr Strains

Strain HfrC used in these experiments has been studied extensively in the pioneer work of Jacob and Wollman[10] and Hayes.[11] HfrC was mated with the F^- strain A288 and selection for the markers Thr^+-Leu^+ was carried out by the usual interrupted mating technic. Samples of the mating mixture were taken at two-minute intervals and treated with a thousandfold excess

of bacteriophage T_6 to immediately lyse the male thus halting the transfer of the chromosome. Following lysis of the males, the samples were then diluted 10^3 fold in broth before plating onto selective media. Thr^+-Leu^+ are measured together since they are extremely close on the genetic map. A plot of the number of recombinants recovered versus time reveals a linear rise in time for Thr^+-Leu^+ starting at about nine minutes (Fig. 1, open circles). I have followed the transfer of several other genetic markers of HfrC and have always obtained linear curves in agreement with the results of Wollman, Jacob, and Hayes.[51] Genetic mapping is based upon the extrapolation of similar straight line plots to the time axis to give the order and time of penetration of genetic characters.



However, in contrast to the prior results with HfrC, when the donor HfrCS101 is crossed to the receptor A288 and treated as previously described, the following results are obtained (Fig. 1, closed circles). Again selection was made for the genes Thr^+-Leu^+. Instead of rising linearly from about 10 minutes on the time axis as predicted from its order of transfer of markers, the curve for Thr^+-Leu^+ selection displays two slopes. A shallow initial slope starts at about 10 minutes and then breaks sharply at about 23 minutes into a second steeper slope. Transfer experiments using other genetic markers of HfrCS101 have consistently shown these biphasic kinetic curves. It should be noticed that the yield of recombinants with the donor HfrC is about 10 fold greater than the yield obtained with HfrCS101. I have performed matings with the two donors until a plateau of recombinant yield is reached and have found that HfrC gives about ten times the number of recombinants as HfrCS101. Therefore, although the scales of recombinant yield for the two donors differ, a comparison of transfer kinetics can still be made.

I shall now discuss briefly some of my results which will not be presented here since a detailed report is being published elsewhere.[52] In other transfer experiments, I have established several important features concerning this unusual chromosome transfer by HfrCS101. These biphasic transfer curves have been obtained not only with other genetic markers but also with other receptor strains indicating that the male is responsible for the peculiar gene entry kinetics. These unusual curves were present in matings performed under a variety of environmental conditions including separating the mating pairs mechanically in a blendor. Also, experiments indicate that these unusual transfer curves are not dependent upon the formation of effective pairs as defined by Clark and Adelberg[13] but rather reflect the properties of chromosome mobilization and transfer inherent in the Hfr. Lastly, I have shown that the initial slopes in the chromosome transfer curves of HfrCS101 represents the true time of entry of the genetic markers. Shortly after I had characterized the transfer properties of HfrCS101, Taylor and Thoman[44] published experimental work dealing with two donors that were identical in direction of transfer and in point-of-origin but that one of them displayed a transfer curve having two slopes. It was concluded on the basis of reproducibility of time of entry that the initial slope was the true in-

dicator of gene transfer. Taylor (personal communication) has found these upward-breaking curves in several other donors and has suggested to me that this transfer phenomena may be a more general property of Hfrs rather than restricted to a few males.

EFFECT OF ACRIDINE ORANGE ON CHROMOSOME TRANSFER

Hirota[25] presented evidence which suggested that the replication of the autonomous sex factor (F) but not the F^+ or Hfr chromosome is inhibited by acridine orange. Following Hirota's observations, Jacob et al.[29] obtained results which showed that acridine orange at a concentration of 25 μg/ml. in the mating mixture does not prevent Hfr and F^- pair formation and conjugation but does inhibit subsequent genetic transfer. These results are in accord with their proposed model in which chromosome transfer is initiated by replication at the integrated sex factor.

In the following experiment, the Hfr strains were mated with the F^- strain A288 and genetic transfer followed both in the presence of 30 μg of acridine orange (AO) per ml. and in the absence of the dye. Samples of the mating mixtures were taken at 45 minutes and treated with an excess of phage T_6 and then selection carried out for the genes Thr^+-Leu^+. The donor and receptor strains were preincubated for 15 minutes with and without the dye prior to mixing in order to eliminate the possibility that differences in dye uptake might be a factor in the obtained results. As is evident in Table 1, at a concentration of 30 μg AO/ml., HfrC gene transfer is inhibited by about 42 per cent while transfer by HfrCS101 is unaffected. These results have been confirmed in similar experiments using other genetic markers. Also, I have done several transfer kinetic experiments using different genetic markers in the presence and absence of acridine orange showing that AO does inhibit chromosome transfer by HfrC but does not affect transfer by HfrCS101. These results would suggest that the replicon of the integrated sex factor in the male strain HfrCS101 is resistant to or protected from inhibition by acridine orange at a concentration of 30 μg AO/ml.

TABLE I. *Effect of AO on Gene Transfer by Hfrs*

CONC. AO (μG/ML.)	NO. OF THR^+-LEU^+	RECOMBINANTS/ML. $\times 10^{-3}$
	HfrC × *A288*	*HfrCS101* × *A288*
0	7300	100
30	4200	104

DISCUSSION

The curves for the kinetics of gene transfer in the donor strain HfrCS101 do not rise linearly from a given point on the time axis. Instead, the plot of recombinants versus time rises at a low linear rate and then at about 13 minutes breaks sharply into a second steep linear slope. The first slope represents the exact time of entry of the genetic markers. This peculiar transfer curve does not appear to be dependent upon any anomaly in formation of effective mating pairs or upon the receptor strain used. Therefore, these unusual curves are a result of the properties of chromosome mobilization and transfer peculiar to the male strain. Recently, similar biphasic transfer curves have been reported for Hfr strains of *E. coli* by Taylor and Thoman.[44] They determined that the initial slope represented the true time of entry of the genetic markers. Taylor proposed that the initial slope represented a small portion of cells that transfer their chromosome at a more rapid rate than the bulk of the donors of the particular Hfr strain. This minority of rapid donors presumably inject their chromosome at the same rate as the cells of the Hfr exhibiting no break in the curve of transfer kinetics.

HfrCS101 was one of the two donors used by Nagata[34] in experiments which indicated that in the Hfr strain replication of the chromosome is sequential starting from the integrated sex factor region and proceeding to the leading end in transfer. However, the experiments of Hirota[25] and Cuzin and Jacob[38] suggest that in the Hfr, the chromosome and integrated sex factor are replicated under the control of the chromosomal replicon. Cuzin and Jacob suggest that the sex factor replicon comes into play only during conjugation and transfer of the chromosome to the receptor cell. As a key

test of this latter suggestion, Jacob et al[29] showed that acridine orange, a dye found to inhibit sex factor replication by Hirota, inhibited chromosome transfer during conjugation by their Hfr strains. However, I have shown that while acridine orange does inhibit gene transfer by strain HfrC, a donor with classical transfer kinetics, the dye does not inhibit chromosome transfer by HfrCS101. Since the sex factor is presumed to play the dominant role in regulating chromosome transfer, it is reasonable to suggest that the sex factor in donor HfrCS101 is responsible this male's being refractory to acridine orange during conjugation. Accepting the premise that the sex factor in HfrCS101 is unusual, how does one explain the transfer behavior of HfrCS101 and Nagata's results of chromosomal replication for this donor?

I believe that the unusual conjugation activity of HfrCS101 may be the result of an unique sex factor regulating mechanism of chromosome mobilization and transfer. The resultant transfer curves of this donor can be explained by assuming that a given cell, in a population of growing HfrCS101, can inject its chromosome by two alternate mechanisms giving rise to what is in effect two donor types with different rates of chromosome transfer within a single Hfr population as suggested by Taylor and Thoman.[44]

I should like to propose the following alternative scheme for conjugation and chromosome transfer in those Hfrs displaying the biphasic transfer kinetics curve. Just prior to attachment between donor and receptor cell, the chromosome of the Hfr may either be at rest or in the process of replication. The chromosome of the Hfr should be in the nonduplicating state in only a very small minority of cells.[53] In these males, contact between Hfr and F^- stimulates the sex factor replicon to begin replication and one of the duplexes being formed is driven into the receptor cell via the model of Jacob et al.[29] This minority of donors account for the fast rate of transfer and the initial linear slope of transfer kinetics. The majority of growing Hfrs have already begun replication of their chromosome starting at the sex factor replicon in the manner suggested by Nagata. In these donors, contact between Hfr and F^- is made; but, the chromosome has to finish duplication and is then transferred. The transfer of the completed duplicate involves a less efficient mechanism for driving the DNA strand into the receptor cell. Therefore, this majority of males have a slower rate of chromosome transfer and account for the second linear slope of transfer kinetics.

SUMMARY

In this report, I have examined the conjugation and transfer kinetics of two Hfr strains of *E. coli* K-12. One of these strains displays unusual transfer curves consisting of two linear components. In addition, this strain is resistant to inhibition by acridine orange during chromosome transfer; while the other donor strain displays classical linear kinetics and is sensitive to inhibition by AO. These results are discussed in relation to the proposed molecular models for chromosome replication and transfer. A new scheme of regulation of chromosome transfer has been put forth to account for the anomalous transfer curves.

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CLINICOPATHOLOGIC CONFERENCE OF THE FRAMINGHAM UNION HOSPITAL

LUKE G. TEDESCHI, M.D.* AND FRANCES COMERFORD, M.D.†

AN 81-year-old white male was admitted to the Framingham Union Hospital for the fifth time in a state of unresponsiveness of about one day's duration. Apart from congenital, bilateral ptosis, partially surgically corrected at the age of 18 years, the patient had been well until 1945, when, at the age of 62, he complained of frequency of micturition. A transurethral resection of the prostate was done in another hospital; the record is unavailable. In 1954, at the age of 71 years, he had a febrile episode, and a heart murmur was heard. A diagnosis of subacute bacterial endocarditis was made, and a three-week course of penicillin and streptomycin was given.

The patient was well, except for a heart murmur, until the early months of 1961, at the age of 78, when he started to complain of weakness and anorexia, particularly to meat. An upper gastrointestinal series and a barium enema at another hospital were reported as normal. He was placed on digitalis, the indication for which was not clear.

Because of the persistence of weakness, he was admitted for the first time to the Framingham Union Hospital, in November of 1961.

On physical examination he was described as a well developed, well nourished, spry, elderly male, in no acute distress. The patient's weight was 137 pounds; blood pressure 120/60; temperature 98°; pulse 72. There was a mild degree of ptosis. The tongue was well papillated. The chest was clear. There was a Grade III mitral systolic murmur and a Grade IV aortic systolic murmur. There were two lipomata of the skin, one in the abdominal wall and the other around the left knee. The chest x-ray revealed clear lung fields and cardiac enlargement with a transverse diameter of 18.5 cm.; that of the chest was 29.5 cm. An upper gastrointestinal series revealed atrophic gastritis. An intravenous pyelogram showed prompt functioning of both kidneys and a post-voiding time film showed considerable residue. An electrocardiogram revealed a normal sinus rhythm with nonspecific ST and T-wave changes, consistent with digitalis effect and/or left ventricular hypertrophy. Complete hemogram was normal. Urine analysis was negative. Albumin was 15 mg. per 100 ml. in a random sample; specific gravity was 1.029; the blood urea nitrogen was 15 mg. per 100 ml.; fasting blood sugar was 103 mg. per 100 ml.; acid phosphatase total was 0.38 unit and the prostatic fraction was 0.04 unit. PBI was 5.4 mg. per 100 ml.; serology was negative. The patient was essentially asymptomatic during his five days of hospitalization, and he was discharged to a nursing home.

He was readmitted four months later because of hematuria. A kidney, ureter and bladder test revealed an 0.5 cm. area of calcification overlying the left kidney. Cystoscopy revealed what was described as cystitis. The

*Associate pathologist, Framingham Union Hospital, Framingham, Massachusetts, and Boston University Medical Center; assistant in pathology, Harvard Medical School, Boston, Massachusetts.

†Assistant in medicine, Boston University School of Medicine, Boston, Massachusetts.

retrograde pyelography revealed a deformity of the left lower major calyx. The discharge diagnosis was cystitis and prostatitis.

He continued to complain of weakness and was re-admitted a year later, in March, 1963. In the interim, the patient had an episode of auricular fibrillation, for which he was put on digitalis. Repeat work-up revealed no change in the physical examination or in the laboratory findings, except for a urinary protein of 500 mg. per 100 ml. in a random sample. No record of the 24-hour urine volume was made. Upon discharge, the patient continued to complain of weakness.

He was admitted to the Lahey Clinic in September of 1963. Except for a ten-pound weight loss, there was no change in the physical findings. The systolic murmur over the precordium was interpreted as representing an interventricular septal defect. Laboratory examination showed normal serum electrolytes. The blood urea nitrogen was 23 mg. per 100 ml.; creatinine was 1.7 mg. per 100 ml.; serum albumin was 2.4 gm. per 100 ml.; globulin 2.5 gm. per 100 ml., with a urinary volume of 1670 ml./24 hours; therefore, the urinary protein per 24 hours was 3.758 grams. A diagnosis of nephrolithiasis and nephrotic syndrome was made; also, atherosclerotic heart disease with mild congestive failure. The possibility of cancer of the prostate was raised. The patient was discharged on digitalis and Prednisone, but he continued to complain of weakness. Because of signs and symptoms of congestive heart failure, Prednisone was discontinued in February, 1964, and diuretics were given.

In May of 1964 the patient was readmitted to the Framingham Union Hospital. The physical findings were the same except for 1 plus pretibial pitting edema. The serum cholesterol was 360 mg. per 100 ml.; blood urea nitrogen 24 mg. per 100 ml.; a random urine sample showed urinary protein of 150 mg. per 100 ml. Complete hemogram was normal. Total protein was 4.2 gm. per 100 ml. and serum electrophoresis revealed the following: albumin 43.7 per cent, $alpha_1$ 7.3 per cent, $alpha_2$ 23.2 per cent, beta 10.6 per cent and gamma globulin 16.2 per cent. The patient was discharged to a nursing home where he became lethargic, refused food, assumed the fetal position and became noisy, for which reason he was taken to his home where, at times, he had attacks described by his daughter-nurse as "seizures," lasting up to one minute. He also had short episodes of unresponsiveness.

The final admission to the Framingham Union Hospital was in October of 1964 because of unresponsiveness of 24 hours' duration. On physical examination, he was rather well nourished, mildly dehydrated and unresponsive. However, there were no positive neurological findings. The vital signs were normal; hematocrit was 30; hemoglobin 9.1 gm. per 100 ml.; white blood count was 12,200 with normal differential; urine showed a specific gravity of 1.008; pH 6.5; urinary protein 400 mg. per 100 ml. The urine sediment was loaded with red blood cells, with occasional white blood cells and 1 to 2 hyaline casts with an occasional granular cast/hpf. Fasting blood sugar was 123 mg. per 100 ml.; globulin 2.3 gm. per 100 ml. Serum electrolytes were as follows: chloride 108, sodium 144, potassium 5.1 and CO_2 21 milliequiv. per liter. The serum cholesterol was 330 mg. per 100 ml. Chest x-ray revealed minimal pulmonary congestion and the previously noted cardiomegaly. The patient was hydrated, became alert, but refused food. His hospital course was that of fluctuation between consciousness and unresponsiveness, with a gradual down-hill course, but at no time were there any positive neurologic findings. The blood urea nitrogen and creatinine remained unchanged; the carbon dioxide, however, fell 14 milliequiv. per liter, while repeat chlorides were 98, sodium 133 and potassium 5.0 milliequiv. per liter.

The patient expired on the 11th hospital day.

Doctor Comerford: The case being discussed today relates to an 81-year-old man who expired following an illness of some considerable duration. As a general approach to illness in the aged, it is worth alluding briefly to a recent study, both statistical and clinical, of 200 consecutive admissions to a geriatric unit.[1] Two major points were made. First, disability in this age group was the result of conventional

physical and mental illness, not of "senility." Secondly, it was stressed that in any given individual, multiple disease processes occurred, frequently unrelated to one another.

To return to the patient, he is described as having congenital ptosis, surgically corrected at the age of 18 years. This is a not uncommon condition and is of no significance in the present instance. The patient was in good health until the age of 62 years, when he developed frequency of micturition. A transurethral resection of the prostate was performed. In the absence of more radical therapy, we must presume that there was no clinical or pathological evidence of malignancy of the prostate. This is confirmed by the patient's many years of subsequent good health. We will therefore assume that the patient had benign prostatic hypertrophy.

At the age of seventy-one, in 1954, the patient had a febrile episode, and a heart murmur was heard. Subacute bacterial endocarditis was diagnosed, and therapy with penicillin and streptomycin was administered for three weeks. The questions that arise here relate to bacteriological confirmation of the diagnosis, and whether any associated clinical features were present. In view of the subsequent story, any findings suggestive of focal or embolic glomerulonephritis would have been of great interest.

The prognosis of subacute bacterial endocarditis in the aged is very poor. In one series of eighty-five cases (mostly males), no patient over the age of sixty-five was living one year after the onset of the illness.[2] Explanations for this included the fact that the causative organisms in the elderly were often staphylococci and gram-negative bacteria, and the disease was commonly associated with genitourinary tract infection. A second recent series confirmed this ominous outlook.[3] So, if this patient did, in fact, have subacute bacterial endocarditis, he was fortunate in the outcome. We cannot make any comment on his cardiac lesion. However, it would not be surprising if his febrile episode was, at least in part, due to chronic genitourinary tract infection.

Following this illness, he continued in good health until early in 1961, when, at the age of seventy-eight, he complained of weakness and anorexia, both of which are nonspecific, and we will assume there was no evidence of neurological or myopathic processes. X-ray studies excluded obvious malignancy of the gastrointestinal tract. Possibly, because these symptoms may occur in heart failure, the patient was treated with digitalis.

In November, 1961, because of persistent weakness, he was admitted to this hospital. The patient was, at that time, a normotensive, healthy-appearing elderly male. The only significant abnormality noted was of the heart, where a Grade III mitral systolic murmur, and a Grade IV aortic systolic murmur were heard.

X-ray studies revealed a number of abnormalities; of significance was definite cardiomegaly, and a considerable post-voiding bladder residue on an intravenous pyelogram. Electrocardiogram changes were nonspecific, and may have been related to digitalis therapy. It is worth remarking on the normal urinalysis on this admission.

At this point, we may assume that the patient had definite cardiac involvement of uncertain etiology.

At the beginning of 1962, the patient was admitted with hematuria. X-ray showed an 0.5 cm. nodule of calcification in relation to the left kidney, a retrograde pyelogram showed deformity of the left lower major calyx, and cystoscopic evidence of inflammation of the bladder.

Doctor Ferrucci:* Review of the x-ray films, at this time, is in general agreement with the previous interpretation. The development of a renal stone, secondary, perhaps, to infection and a mild degree of obstruction, would account for these findings. The generalized cardiac enlargement deserves consideration.

Doctor Comerford: Over the next year, the patient continued to complain of weakness, and was admitted again for re-evaluation in March, 1963. In the interim, he had had an episode of atrial fibrillation. Physical examination, and with one exception, laboratory studies, were unchanged. Thus, the process responsible for this clinical picture would certainly appear to be in-

*Radiologist, Framingham Union Hospital.

sidious and of a slow development. The one abnormality that had occurred since the last admission was that of significant proteinuria. If one may extrapolate, the patient, at this time, was losing from 5 to 7 grams of protein daily in his urine. This information is of considerable importance.

Six months later, in September of 1963, the patient was admitted to the Lahey Clinic. There had been a ten-pound weight loss. The systolic murmur was considered to be due to an interventricular septal defect. This may be a difficult diagnosis to make on purely clinical grounds. However, it is of interest to note that minor degrees may be associated with prolonged survival and no disability.[4] The laboratory values showed some elevation of serum creatinine, hypoalbuminemia, and a 24-hour urine protein of 3.8 grams. The diagnoses, on discharge, were: nephrolithiasis, nephrotic syndrome, and arteriosclerotic heart disease with mild congestive failure. Discharge medications were digitalis and Prednisone, the latter being continued for five months.

Two points may be considered here. First, the question of the criteria to be utilized in making a diagnosis of the nephrotic syndrome is obviously relevant. The classical features, proteinuria, hypoalbuminemia, hypercholesterolemia, and edema are well known. However, in a given case, not all may be present, and disagreement over quantitation may occur. In the literature, various levels of proteinuria have been proposed, from 14 grams per 24 hours down. A recent report from Boston utilized a level of 5 grams of proteinuria per 24 hours.[5] Berman and Schreiner[6] proposed, as minimal criteria, "the excretion into the urine of 2.5 or more grams of protein per day, and doubly refractile or oval fat bodies." In this instance, with documented proteinuria of over 3.5 grams per 24 hours, and knowing that this was present, in all probability, for six or more months, one may reasonably assume that the patient had, indeed, a nephrotic syndrome.

The second point we may briefly consider here is the therapy of the nephrotic syndrome. This patient was started on steroid therapy as soon as the diagnosis was made. Referring again to the study of Nesson et al.[5] there is apparently a definite, though not marked, advantage in the use of steroids in this condition. There is a strong suggestion that improvement is related to the initial histologic picture; cases showing only minimal hypercellularity tended to go into rapid remission, while those with more definite histologic evidence of abnormality do not. (It is notable that 25 per cent of patients treated with steroids develop major complications due to this therapy, and there was one death.) These results substantiate those of Burch, Pearl and Sternberg.[7] In both these studies, the nephrotic syndrome, due to systemic disease, was excluded. The potential hazards of steroid therapy, and the value of renal biopsy both as a diagnostic procedure, and in regards to prognosis are factors that must be kept in mind in the assessment of all cases complicated by the nephrotic syndrome.

To return to the patient, nine months later he was again admitted to this hospital. On this occasion, he was noted to have 1 plus pretibial edema. He had persistent proteinuria, a relatively normal blood urea nitrogen, and some elevation of serum cholesterol. The serum albumin was 2.4 grams per 100 ml., and serum electrophoresis showed an elevated alpha$_2$ globulin, such as is seen not infrequently in the nephrotic syndrome.

Following this, he had lethargy, agitation, and episodic unresponsiveness. In addition, he is said to have had seizures. His final admission to the Framingham Union Hospital was in October of 1964. On examination, he was unresponsive and mildly dehydrated. Laboratory studies revealed severe uremia, with anemia. Urinalysis showed hematuria and continued proteinuria. He developed acidosis and expired on the 11th hospital day.

In summary, we have an elderly man who had nonspecific complaints of weakness for two years, went on to develop a nephrotic syndrome, and 18 months later died of renal failure. In addition, he had: urinary tract disease with mild prostatic obstruction, and probable nephrolithiasis and infection; cardiovascular disease with cardiomegaly, systolic murmurs, arrhythmia, and congestive

heart failure; and possible convulsive episodes for some months prior to death.

In considering the etiology of this patient's disease, the most profitable approach relates to the cause of the nephrotic syndrome. We know that this was not present at the time of the first admission in 1961. What disease process, in this age group, might produce this, and possibly the other features of this man's illness? In this connection, the article by Kark et al.[8] is worthwhile reading.

I will first exclude the more common causes of the nephrotic syndrome, such as glomerulonephritis, and lipoid nephrosis, as being unusual in this age group, and not offering an explanation for the cardiac involvement.

Systemic lupus erythematosus may sometimes be a diagnostic problem. While it is typically a disease of young women, it may occur in older males. Again, the associated findings such as a rash, arthritis and serositis are usually prominent, but may be completely absent. A recent report describes two cases of the nephrotic syndrome in males, where the diagnosis of systemic lupus erythematosus was made only at autopsy.[9] This is, however, quite uncommon, and I will dismiss systemic lupus erythematosus from serious consideration.

Diabetic nephropathy is a common cause of the nephrotic syndrome. In this case, there is no real evidence for diabetes, other than a single terminal elevation of blood sugar. Had the patient had diabetes mellitus, the steroid therapy should have provoked some overt positive findings.

The administration of various drugs, and various hypersensitivity states have been associated with the nephrotic syndrome. There is no evidence for these factors in the present case.

The possibility that subacute bacterial endocarditis was the cause of the nephrotic syndrome in the present case must be seriously considered. The patient had a past history of what was described as subacute bacterial endocarditis, a definite heart murmur attributed to ventricular septal defect (the most common congenital lesion occurring with subacute bacterial endocarditis) and a history of vague complaints, such as are frequently seen in subacute bacterial endocarditis. Renal involvement might have occurred during the episode of 1954, and progressed gradually over the years. The negative urinalysis in 1961, and the length of time makes this unlikely. The other possibility is that a second episode of subacute bacterial endocarditis occurred in 1961. This, again, is also most unlikely, in the absence of fever, and in view of the relatively benign course.

Renal vein thrombosis is a cause of the nephrotic syndrome that cannot be excluded in the present case. It is occasionally associated with flank pain, but may also occur silently.

Finally, there is a further possible cause for the nephrotic syndrome that must be considered. In reviewing reports on the nephrotic syndrome, I was impressed by the low incidence of the condition in those over the age of sixty-five years. But there is one condition that is more common in later life, is found perhaps more frequently in males, and is a common cause of the nephrotic syndrome. This is amyloidosis.[10] This diagnosis is often unsuspected until renal biopsy or autopsy. The absence of hypertension, and the rather rapid course from onset of the nephrotic syndrome to death, while by no means specific, would tend to support this diagnosis. This patient's cardiac involvement pre-dated his renal involvement, at least clinically. Murmurs are said to occur in one-third of cases of amyloid heart disease; there is usually diffuse cardiac enlargement, and arrhythmias are common. In this case, the pattern of involvement is obviously different from that seen in the familial amyloid cardiomyopathies, where severe heart failure ends in death in middle age.[11] I suspect it will also differ from the localized senile cardiac amyloid found quite frequently at autopsy in the aged, and which is probably of no clinical significance.[12] There are many reports of cases, however, of nonfamilial primary amyloidosis with significant cardiac involvement.[13,14]

Finally, in view of the history of the seizures late in the disease, one might speculate that these were related to the presence of Alzheimer's plaques in the brain. This lesion was considered by Richardson to be a

possible cause of epilepsy in the aged.[15] While it is not related, as far as is known, to systemic amyloidosis, it is of interest that recent studies indicate that by light and histochemical and electron microscopy,[16,17] it is identical to amyloid occurring elsewhere.

In the present case, there is no evidence of the diseases which may lead to the development of secondary amyloidosis, such as chronic bacterial infection, rheumatoid arthritis or myeloma.

There is considerable evidence that the incidence of amyloid is greater than is generally assumed, and may perhaps be increasing. A definite diagnosis of amyloidosis rests on the demonstration of the characteristic appearance and staining reaction of involved tissues. While biopsy of the clinically involved organs, such as the kidney in the present case, is desirable, examination of more accessible tissue will often reveal the typical changes. A recent study[18] showed that in amyloidosis of all types, some seventy per cent of cases had positive rectal biopsies, as opposed to eighty per cent positive on renal biopsy, forty per cent positive on liver biopsy and a lesser percentage positive with gingival biopsy. It should be noted that bleeding problems occur with increased frequency in amyloidosis, and that biopsy of the kidney, and particularly the liver, is associated with some increase in risk.

From a clinical viewpoint, the diagnosis of amyloidosis should be considered in cases with disease involving several organs, particularly heart, kidney and liver. The presence of a predisposing disease is obviously important, and there is increased awareness of the importance of ethnic background. There is no completely reliable clinical test, though the Congo Red test can be of value.[19]

Finally, there is no effective therapy now available for this condition. The study of Maxwell, Adams and Goldman[10] cited above, indicated that steroids were not helpful in the nephrotic syndrome due to amyloidosis.

CLINICAL DIAGNOSES

Nephrotic Syndrome.

Rheumatic Heart Disease and Congestive Failure.

Cerebral Arteriosclerosis.

DOCTOR COMERFORD'S DIAGNOSES

Primary Amyloidosis, with Renal and Cardiac Involvement.

Question of Alzheimer's Pre-senile Dementia.

Benign Prostatic Hypertrophy with Nephrolithiasis and Urinary-Tract Infection.

Doctor Tedeschi: Autopsy revealed a globular-shaped enlarged heart weighing 520 grams. There was marked hypertrophy of the walls of the left ventricle and prominent dilatation of the right ventricle, associated with an enlarged tricuspid orifice (17.5 cm. in opened state); the aortic valve showed moderate thickening of the cusps, mostly due to atheromatous and fibrous plaques. No evidence of valvular changes consistent with healed or active rheumatic valvulitis were noted.

Approximately 200 cc. of clear, lemon-colored fluid were present in each pleural cavity, and the lungs were edematous and congested. These findings are consistent with recent heart failure.

The left kidney weighed 200 grams. It was the site of a poorly demarcated, soft, friable, golden-yellow mass, 5 x 3 x 2 cm., which occupied most of the lower pole (Fig. 1). This mass impinged upon, but did not invade, the calices, and both pelves and ureters were essentially normal. The upper pole of the same kidney was firm, translucent, reddish-brown, with poor demarcation between cortex and medulla and obscuring of normal markings. Microscopic examination showed the mass to possess the unequivocal characteristics of a well-differentiated, clear-cell renal carcinoma. The right kidney weighed 160 grams. It was firm and reddish-brown in some areas, pale in some other areas, and the cortex was coarsely granular with a prominent translucent appearance (Fig. 2).

Liver and spleen were not enlarged and weighed 1500 and 140 grams respectively. However, both organs were firmer than normally, with an unusual translucency, which made the prosector to suspect amyloid disease. This was confirmed at microscopic evaluation of the section (Fig. 3).

Figure 1 — Photograph of left kidney, showing a poorly demarcated, lobulated mass, diagnosed as clear-cell renal carcinoma.

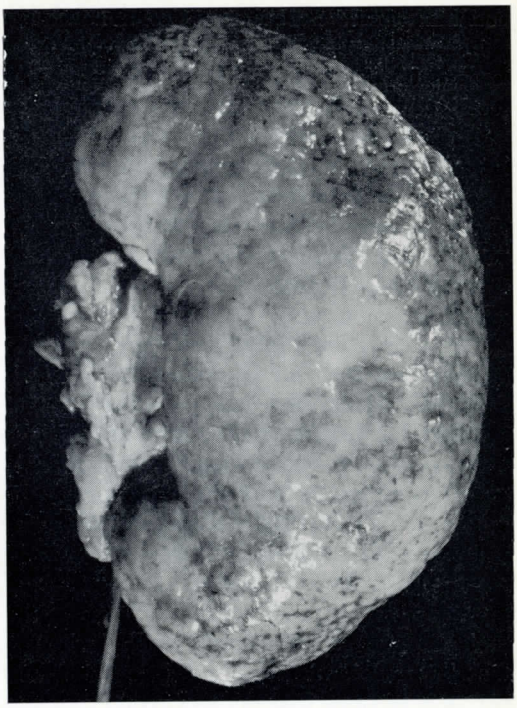

Figure 2 — Photograph of right kidney, showing a coarsely granular cortex with a prominent translucent appearance which histologically revealed diffuse amyloid deposition.

Liver, spleen, pancreas, heart, both kidneys and adrenals, showed an irregular deposition of interstitial, extracellular, amorphous, structureless, and faintly eosinophilic substance with characteristics of "hyaline." The areas involved in the individual organs displayed associated atrophy of adjacent cells. This hyaline precipitate was most abundant in the kidneys, involving stroma of cortex and medulla, as well as vessel walls and glomerular tufts. It stained metachromatically with Congo Red and Gentian Violet, a tinctorial property which is considered characteristic of amyloid.

No evidence of amyloid deposition was found in sections from the tongue and random samples of skeletal muscle. Careful evaluation of sternal and spinal bone marrow consented to rule out the coexistence of multiple myeloma. Amyloidosis occurs in approximately thirteen to fifteen per cent of all patients with multiple myeloma.

If one accepts the distinction between primary and secondary amyloidosis as two separate clinical-pathological entities, with distinct histochemical characteristics and organ distribution, the pattern of organ involvement in our case is more in keeping with a secondary or parenchymatous-type of amyloid disease, rather than a mesodermal or primary type. Secondary amyloidosis is usually seen with long-standing wasting disease, such as tuberculosis, bronchiectasis, rheumatoid arthritis, osteomyelitis, regional ileitis, etc. However, none of these conditions were present in the case under consideration.

The association of amyloid disease and renal-cell carcinoma, has been recently pointed out in the literature; apparently, renal carcinoma is the most frequent neoplasm seen in conjunction with this condition.[20,21] Although the link between renal carcinoma and amyloid is still in the realm of speculation, the concurrence of the two conditions in our patient adds interest to the case.

The chemical composition of amyloid has

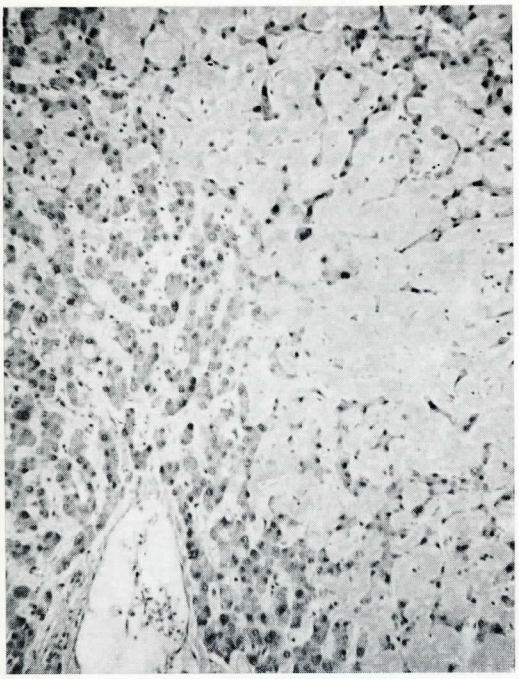

Figure 3 — Section of liver showing disruption of lobular architecture, atrophy of hepatic cells, and replacement of large portions of hepatic parenchyma by amyloid substance. H. E. Stain, X350

evoked considerable study since 1853, when Virchow[22] noted that this substance elicited a starch-like reaction to iodine and sulphuric acid; hence, the term "amyloid." Amyloid, by chemical and histochemical analysis, consists primarily of protein, with varying amounts of acid mucopolysaccharide material. Electron microscopy studies have shown that it possesses a fibrillar ultrastructure, the fibrils being composed of double-coiled protein chains, holding gamma globulin molecules.

Although the basic mechanisms involved in the production and deposition of amyloid are still a matter of considerable controversy, available data point very strongly to an antigen-antibody reaction, resulting in the deposition of circulating protein mucopolysaccharide complexes. Both degenerative changes in the connective tissue and an abnormal secretion of the reticuloendothelial cells have been advocated to explain the presence, in the blood stream, of protein mucopolysaccharide complexes in high concentration.

The complexity of the problem is further shown by the recent observation that a particular strain of mice (A) develops amyloidosis spontaneously as a function of age. The onset of amyloidosis is associated with an elevation of beta globulins in the blood serum and with the detection of a protein mucopolysaccharide complex in the urine. As the animal grows older, the characteristic tinctorial properties of amyloid are progressively lost and finally the material assumes the properties of "hyaline."[23]

To return to our patient, the primary cause of his demise is attributed to systemic amyloidosis, involving numerous organs, primarily the kidneys, with ensuing renal failure and nephrotic syndrome. In the absence of any other underlying cause, one wonders on the possible relationships between amyloid disease and the coexistent renal carcinoma. The coincidence of the two conditions has already been stressed in the literature.

Unfortunately, permission to examine the central nervous system was not obtained and we, therefore, could not correlate Doctor Comerford's speculation as to the presence of Alzheimer's plaques in the brain.

PATHOLOGIC DIAGNOSES

Amyloid Disease with Involvement of Heart, Liver, Spleen, Pancreas, Kidneys, and Adrenals.

Clear-cell Carcinoma, Left Kidney.

Cardiac Hypertrophy, Biventricular, with Atheromatous Thickening, Aortic Valve.

Congestion and Edema of Lungs, Bilateral, Diffuse.

Serous Pleural Effusion, Bilateral.

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EDITORIAL

ADMISSIONS TO BOSTON UNIVERSITY SCHOOL OF MEDICINE, 1965

At a recent Faculty meeting of the School of Medicine a report was made on the work of the Admissions Committee in 1965. Several members have suggested that the facts given would be of interest to a wider audience and particularly to Alumni. For this reason I choose this topic for the December Editorial.

The present Admissions Committee consists of Drs. Murray Freed, Vincent Lanzoni, William Malamud, William McNary, and George Whitelaw with the Assistant Dean as Chairman. The Committee met 29 times between November, 1964 and May, 1965 spending about 60 hours in meetings. Prior to each meeting each member takes home about 15 applicants' folders for close study before the following meeting. At the meeting each member votes secretly assessing each applicant, and the votes are totaled and the applicants ranged in order of priority on the Waiting List, which is added to each week and the acceptances are drawn from the top of this list. Study of the folders at home takes about two hours a week and represents about 60 hours of work in the year. Any candidate whose intellectual record makes admission worth considering, is interviewed by a member of the Committee. The time spent by each member interviewing candidates is about 50 hours per year. Thus each member of the Committee gives about 170 hours total time to this work, and it is a pleasure to have the chance to acknowledge this valuable work for the Medical School in public and print. Also I must mention the valuable work of Mrs. Anne Gowing, the Registrar, and her secretaries in the preparation of folders and collection of information. Early in the new year, each year, when applications for the Six-Year Program are considered, the Committee is joined by Professor Mason, Miss Eleanor Tyler and Mr. Leach, from the College of Liberal Arts, who give us invaluable aid in selecting students to enter the Six-Year Program.

Now a few statistics for the past year. 2237 application forms and 3018 bulletins were sent out. 1097 students applied, and 83 were invited. 45 of these withdrew after acceptance and 38 were finally accepted, with 34 students from the Six-Year Program making up a class of 72 students. 168 applicants withdrew before action had been taken on their folders.

284 students were interviewed for the Four-Year Program and 103 for the Six-Year Program. Interviews are given to any candidate whose record makes him a possible acceptance, and in addition, to any student recommended by Faculty, Alumni, or friends of the school whatever his record.

In addition to Boston University which supplied the 34 students for the Six-Year Program, the following colleges were represented in the class of 1968: Harvard, Columbia, Brandeis, Williams, Amherst, Brown, Adelphi, Albion, Boston College, Clark, Dartmouth, University of Copenhagen, DePauw, Emmanuel, McGill, University of Michigan, University of Notre Dame, University of Pennsylvania, University of

Pittsburgh, Princeton, Rutgers, Tufts, Vassar, University of Vermont and Yale.

It is pertinent here to ask ourselves why students choose to come to B.U.S.M. The reasons most often given are that the school is in Boston, has fine clinical facilities, the class is fairly small, and there is close student-faculty contact. Students wisely do not worry too much about old-fashioned buildings if the teaching is good: however, it will be an asset to have the modern Instructional Building planned for the immediate future. The reputation built up by Alumni of the school plays no small part in influencing future students to choose this school, and above all the devotion of the Faculty to good teaching is paramount.

Just a word about the general sentiments of the Committee on Admissions. We are trying to pick students who will make the best physicians, not necessarily the best medical students. We want as far as possible a balanced class with both clinically and research-oriented students. We want all our selections to graduate and our ideal class would have no drop-outs. This means that we try to avoid taking any student who has an inadequate knowledge of general chemistry, organic chemistry, physics or biology lest he fail in the first two years despite high character and motivation. Students are selected on the basis of merit, in the widest sense of the term, and one need hardly mention, regardless of race, color, class or creed. By "merit in the widest sense of the word" we all agree that character, motivation, drive, and personality may be more important than intellectual level alone. The B student with these qualities, in our experience, does better than the A student without them. Finally I would stress that *other things being equal,* we give preference to sons of Alumni or faculty recommendations but the student of highest merit always takes preference. May I stress to Alumni and Faculty who may be asked to advise possible applicants of whatever caliber, that we will always grant these students an interview and give them whatever advice is appropriate to help them enter medical school.

The Admissions Committee feels honored to play its part in preserving and trying to improve the quality of Boston University School of Medicine.

L.D.O.

ANNOUNCEMENT

Nelson Foss Evans, currently Director of the American University Hospital in Beirut, Lebanon, will succeed Dr. Philip D. Bonnet as Administrator of Boston University Medical Center's University Hospital on January 1, 1966.

Prior to his appointment in Beirut, Mr. Evans served as Administrator of the University of Arkansas Medical Center's University Hospital.

ITEMS OF INTEREST

The National Institutes of Health awarded $1,405,000 to the nation's first Aphasia Center.

The new Center will be located jointly in the Medical Center's University Hospital Outpatient Department, Boston Veterans Administration Hospital and the Joseph P. Kennedy, Jr. Memorial Hospital. It will be staffed by a group of senior researchers such as Drs. Norman Geschwind, Harold Goodglass, Davis Howes, and Charles A. Kane.

The objectives of the new Center will be research in disturbances of language and related disorders. The major areas of study will include clinical neurological investigations, anatomical studies, neuropsychological studies of aphasia, dominance in children and adults, and studies of other language problems.

A bill striving to remove the major legal stumbling blocks to the advancement of medical science will be filed next week for introduction in the 1966 session of the Massachusetts legislature.

The bill, designed to facilitate the donation of anatomic organs and tissues, was drafted by Dean William J. Curran, director of the Boston University Law-Medicine In-

stitute and MetroCenter; Neil L. Chayet, assistant professor of legal medicine at the Institute; and Rep. James Wheeler of Westwood. Representative Wheeler will submit the bill.

The purpose of the legislation will be to facilitate gifts of bodies and/or body parts for use in study in certified medical schools and to allow the transfer of human tissues for use in living persons.

Under the provisions of the bill any person 21 years old or older can, in a will or a separate document, leave his body, organs and/or tissues to medicine. The document must be witnessed by three persons.

A substance thought to be insulin is being secreted by transplanted pancreatic tissue.

This conclusion, generated by a Boston University research project and released at the American Medical Association's Clinical Convention in Philadelphia, appears to be an important step in human diabetes research although this series of successful transplantations occurred in cheek pouches of hamsters.

A team from Boston University's Biological Science Center announced their findings in an exhibit titled The Clinical Application of Pancreatic Transplants. The research has been supported largely by funds from U.S. Public Health Service grants and the Green Shoe-Stride-Rite Charitable Foundation.

The team consists of Samuel B. Beaser, M.D., research associate in Biology, and co-investigator I. Alden Macchi, Ph.D., professor of biology, project director and chief investigator and Matthew F. Sak, Ph.D., assistant professor of science, and research associate.

In the project, a few millimeters of pancreatic tissue obtained from the newborn hamster, were inserted within the thin inner layers of the cheek pouch of an adult hamster which had been rendered diabetic. Several transplants were made into each pouch.

Post transplantation treatment with sulfonylurea drugs then proved such a stimulant to pancreatic growth that the BU researchers were able to implant more successfully a neo-natal pancreas into non-diabetic hamsters.

After 30 days, the mature transplants were removed and, according to the paper which accompanies the exhibit, were shown to proluce *in vitro* a chemical substance possessing some of the characteristics of naturally secreted insulin, as measured by standard measures.

The importance of this work lies in several areas. It provided a means of growing relatively pure beta cells of the mammalian pancreas. It also indicated that the means of promoting this growth was the result of an almost unique circumstance: the combination of stimulation of secretion and cytostructural growth of a mammalian tissue by a non-biological synthetic pharmaceutical agent. This biological system allowed the quantification of the relative potency of two such agents (the sulfonylureas, tolbutamide and chlorpropamide). It was noted also that the latter drug which is more potent clinically in the treatment of human diabetes mellitus had a measure of superiority by this type of biological measurement.

Recently Published

Current Concepts in Therapy Volume VII

The seventh volume of *Current Concepts in Therapy* includes those articles published in the *Journal* in 1963. It includes —

Hemolytic Anemia
Active Immunizations
Bronchial Asthma
Education of Diabetic Patient
Management of Myasthenia Gravis

Hazards to Health Volume II

The second volume of *Hazards to Health* includes those articles published in the *Journal* in 1962. A partial list of the contents includes —

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Epoxy Resins
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Work in Hot Weather
Chronic Meprobamate Intoxication

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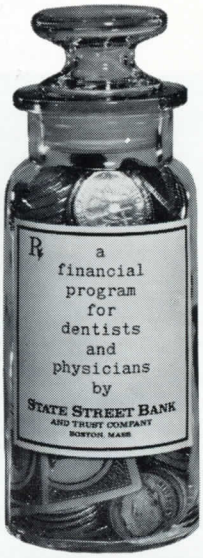

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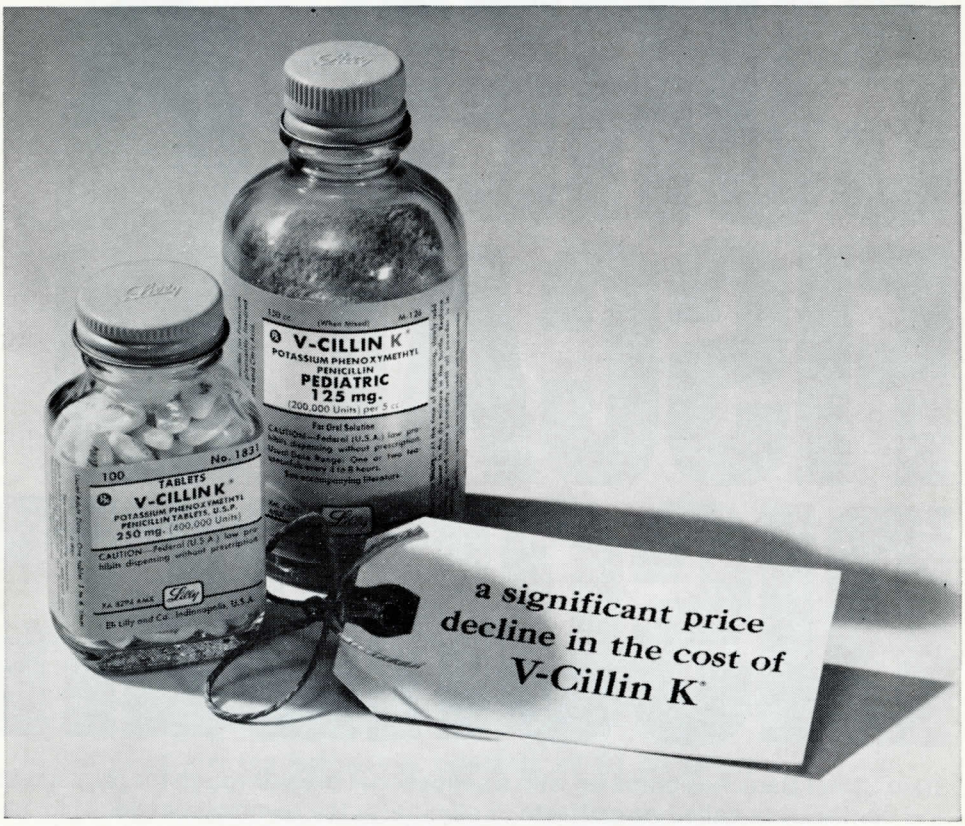

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